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Stereocomplexity and Stereoselective Synthesis of Triamine Molecules Bearing Four Chiral Carbon Centers: Stereodifferentiated Preparation of All 10 Stereoisomers of 2,6-Bis[1-(1-phenylethylamino)ethyl]pyridines

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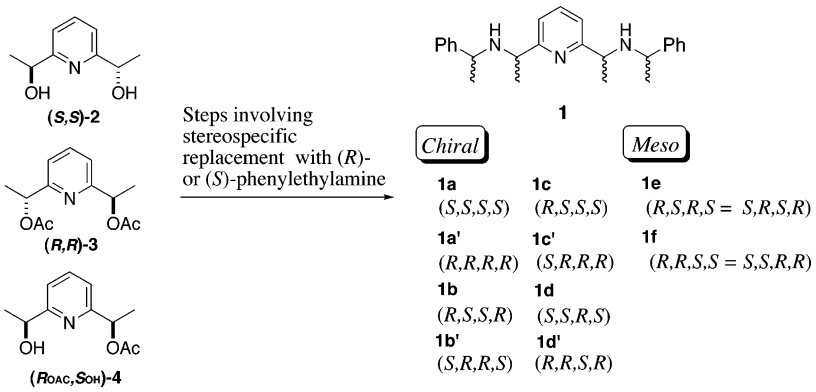

Compounds (*S*,*S*)-2,6-bis(1-hydroxyethyl)pyridine, (*R*,*R*)-2,6-bis(1-acetoxyethyl)pyridine, and (1*R*,1′*S*)-2-(1-acetoxyethyl)-6-(1′-hydroxyethyl)pyridine were obtained by lipase-catalyzed kinetic acetylation of 2,6-bis(1-hydroxyethyl)pyridine as enantiomerically pure forms. The stereospecific replacement of hydroxy groups with (*R*)-phenylethylamine or (*S*)-phenylethylamine via its methanesulfonate or toluenesulfonate simultaneously or stepwise afforded all the stereoisomers of **1**. Stereospecific preparation of all the 10 possible stereoisomers of 2,6-bis[1-(1-phenylethylamino)ethyl]pyridines **1a**−**f** was achieved. Triamine **1b** reacted with $ZnCl_2$ to form Zn−triamine complex **16**, the structure of which was determined by X-ray crystallographic analysis.

Introduction

The chirality and stereocomplexity of natural and unnatural molecules have attracted much attention.[1] Related to them, the molecular symmetry and asymmetry of organic compounds have been an important subject in organic chemistry.[2] When the molecule possesses multiple *n*-chiral centers, 2^n of stereoisomers are present. If we wish to obtain only one of the stereoisomers, chromatographic separation by HPLC, recrystallization or stereoselective synthesis is undertaken. Although remarkable technical advances and developments in separation of organic compounds[3] allow us to isolate one enantiomer or diastereomer in complex molecules, this still remains difficult for specific compounds. In such cases, stereoselective synthesis is highly desired with a combination of effective separation techniques.

We have been interested in such symmetric and asymmetric organic molecules possessing multichiral centers. In this paper, we report the stereodefined synthesis of 10 2,6-bis[1-(1-phenylethylamino)ethyl]pyridines **1a**−**f** in a stereochemically pure form.

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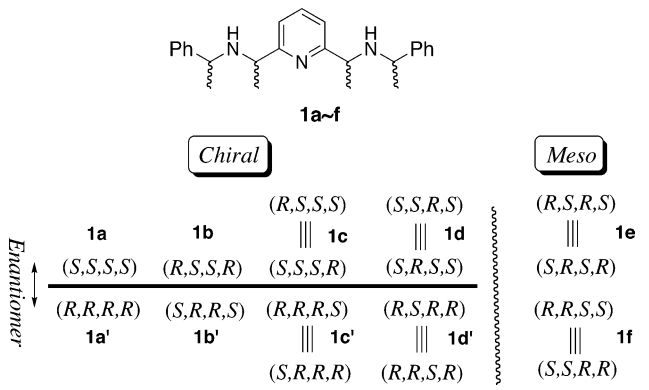


FIGURE 1. Ten stereoisomers of 2,6-bis[1-(1-phenylethylamino)ethyl]-pyridine.

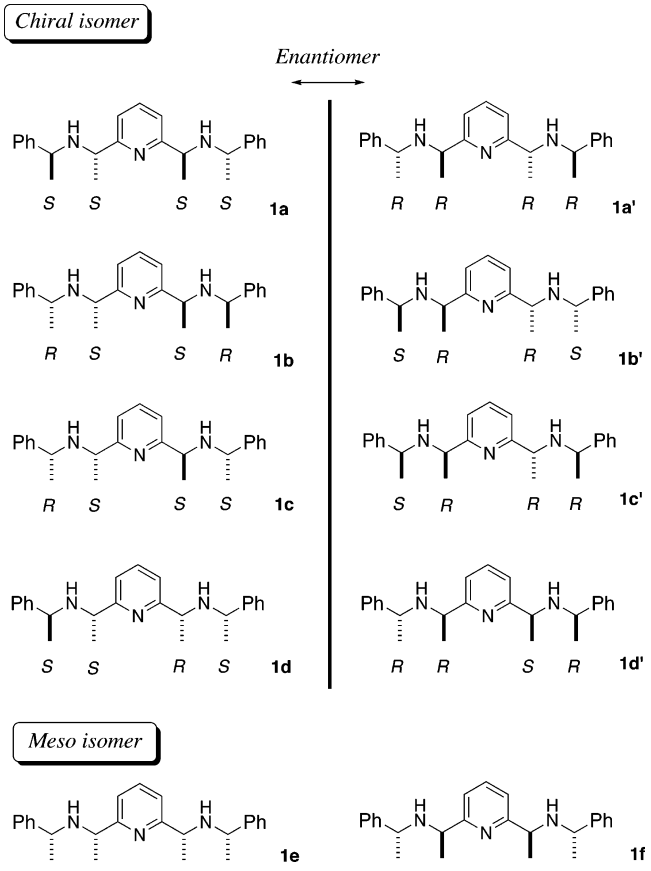
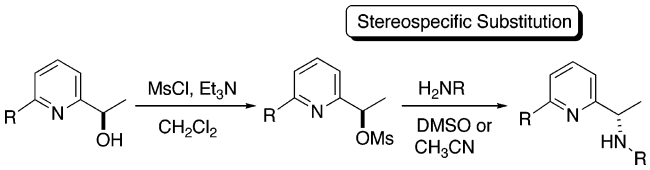


FIGURE 2. Structures of **1a**−**f**.

Results and Discussion

Since four chiral centers exist in **1**, 16 (2^4) stereoisomers are available theoretically.[4] However, due to the symmetry of the molecule, eight chiral diastereoisomers involving 4 enantiomeric pairs of **1a**,**a**′, **1b**,**b**′, **1c**,**c**′, and **1d**,**d**′ and two meso isomers **1e** and **1f** actually exist, the structures of which are shown in Figures 1 and 2. Although all of the diastereomers and enantiomers of **1** were prepared by three steps, including the nonselective reduction of 2,6-bisacetylpyridine with $NaBH_4$, mesylation with methanesulfonyl chloride, and the substitution of mesylate with racemic 1-phenylethylamine. However, they could not be separated completely by HPLC or GPC. Therefore, we decided to try to stereoselectively synthesize them.

SCHEME 1



Tactics for the Construction of Chiral Centers and Synthetic Strategy for 1a−f. Previously, we reported that the substitution reaction of chiral 1-(2-pyridinyl)ethyl methanesulfonates with amine nucleophiles[5] proceeds stereospecifically to give the stereoinversion product via an S_N2 process exclusively, as shown in Scheme 1. Various kinds of optically pure 1-(2-pyridinyl)ethylamines were synthesized from the corresponding optically pure alcohol in two steps: (i) methansulfonylation and (ii) stereospecific substitution at the benzylic position. The starting chiral alcohol could be prepared very efficiently by lipase-catalyzed kinetic acetylation of racemic alcohol.[6]

Therefore, if we can obtain chiral 2,6-bis(1-hydroxyethyl)-pyridines, **(*R*,*R*)-2**, **(*S*,*S*)-2**, ***meso*-2**, and (1′*R*,1″*S*)-2-(1′-acetoxyethyl)-6-(1″-hydroxyethyl)pyridine **(*R*OAc,*S*OH)-4** by lipase-catalyzed kinetic acetylation[7] and they are subject to the stereospecific substituted reaction via their methanesulfonates, compounds **1a**−**f** will be synthesized stereoselectively, as shown in Scheme 2. Namely, their starting materials will be these chiral **(*R*,*R*)-2**, **(*S*,*S*)-2**, **(*R*OAc,*S*OH)-4**, and ***meso*-2**. Substitution reactions of the corresponding mesylate with (*S*)-(−)-phenylethylamine (X in Scheme 2) or (*R*)-(+)-phenylethylamine (Y in Scheme 2) give **1a**−**f** stepwise or simultaneously.

Preparation of 2,6-Bis(1-hydroxyethyl)pyridines.[7] A diastereomixture of 2,6-bis(1-hydroxyethyl)pyridine **2** was prepared by reduction of 2,6-bisacetylpyridine with $NaBH_4$. A kinetic acetylation of **2** with vinyl acetate in the presence of *Candida antarctica* lipase gave diacetate **(*R*,*R*)-3** in 23% yield, monoacetate **(*R*OAc,*S*OH)-4** in 45% yield and the recovery of **(*S*,*S*)-2** in 23% yield. Potassium carbonate promoted methanolysis of **(*R*,*R*)-3** gave diol **(*R*,*R*)-2** in quantitative yield. On the other hand, methanolysis of monoacetate **(*R*OAc,*S*OH)-4** gave ***meso*-2** in 79% yield (Scheme 3).

Preparation of 1a−c from (*R*,*R*)-2 and 1a′, 1b′, and 1c′ from (*S*,*S*)-2. Mesylation of **(*R*,*R*)-2** in CH_2Cl_2 gave dimesylate **(*R*,*R*)-5** in quantitative yield. Substitution of the mesylate with (*S*)-phenylethylamine in the presence of *N*,*N*′-diisopropylethy-

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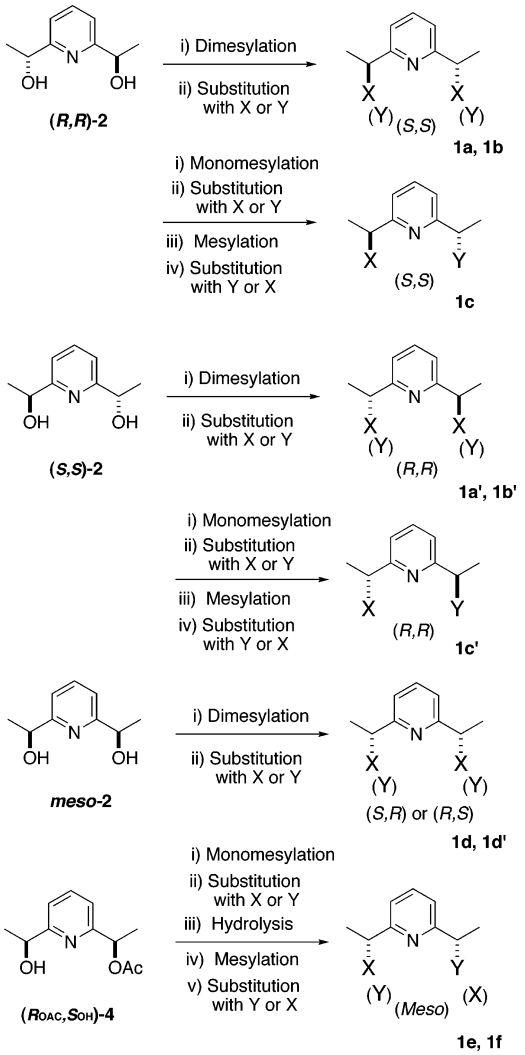
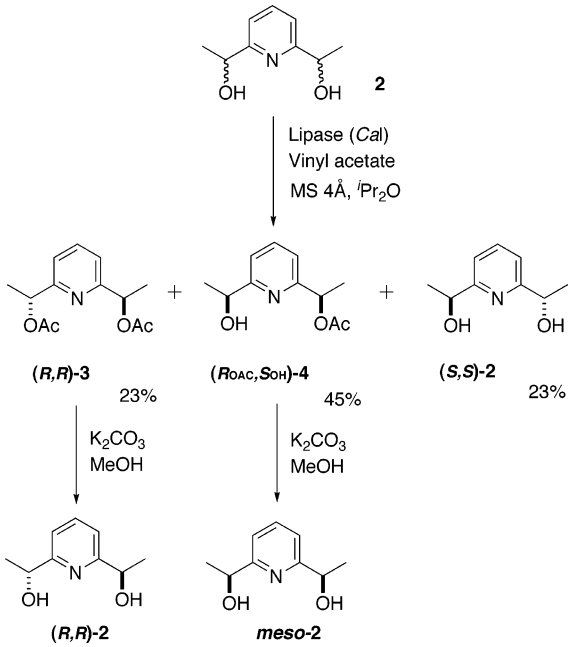
SCHEME 2. Synthetic Plan for 1a−f



lamine in CH_3CN at 60 °C afforded **1a** in 70% yield, while that with (*R*)-phenylethylamine afforded **1b** in 75% yield. Tosylation of **(*R*,*R*)-2** was carried out at room temperature in CH_2Cl_2 to give **6** in 44% yield selectively at 50% conversion of the reaction, though the formation of ditosylate was increased when reaction time was prolonged. Substitution of the tosylate with (*R*)-phenylethylamine gave **7** in 99% yield. Replacement of the remaining hydroxy group with (*S*)-phenylethylamine was performed via the corresponding tosylate **8** to give **1c** in 61% yield in two steps. In a similar manner, enantiomers of **1a′** and **1b′** were synthesized via dimesylate **(*S*,*S*)-5** in 81% and 97% yields respectively. Compound **1c′** was derived from **(*S*,*S*)-2** in four steps. The enantiomer **6′** derived from **(*S*,*S*)-2** by monotosylation reacted with (*R*)-phenylethylamine to give **9** in 91% yield. After tosylation of the remaining alcohol, the substitution of the tosylate **10** with (*S*)-phenylethylamine afforded **1c′** in 68% yield in two steps (Scheme 4).

Preparation of 1d and 1d′ from *meso*-2. The synthesis of **1d** and **1d′** from ***meso*-2** is shown in Scheme 5. Dimesylation of ***meso*-2** gave ***meso*-5** quantitatively. Substitution of the mesylates with (*S*)-phenylethylamine and with (*R*)-phenylethylamine in the presence of *N*,*N*′-diisopropylethylamine in CH_3CN at 60 °C gave optically pure **1d** and **1d′** in 75% and 63% yields, respectively.

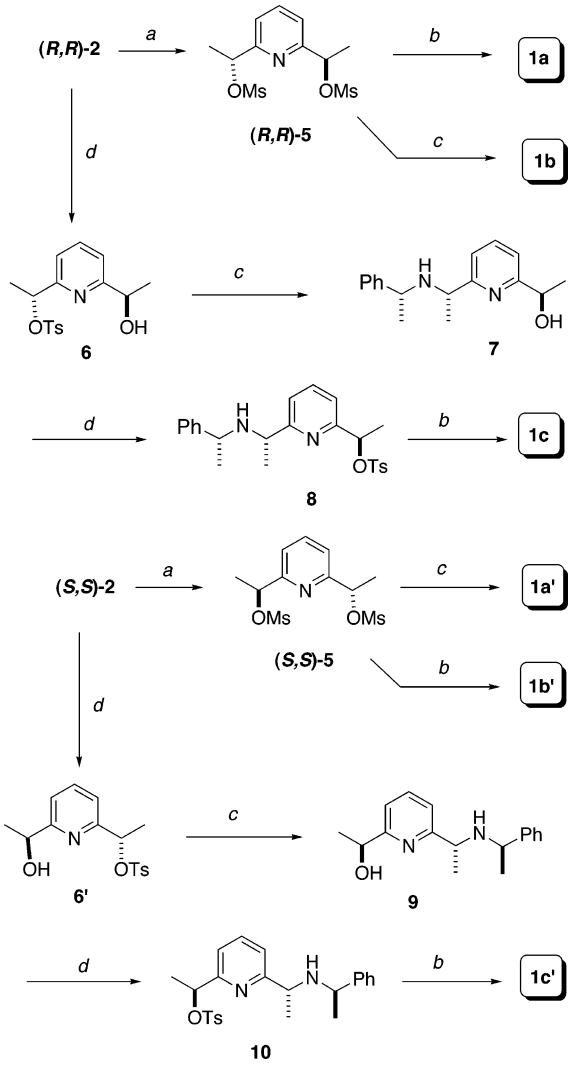
SCHEME 3



Preparation of *meso*-Isomers 1e and 1f from (*R*OAc, *S*OH)-4. The synthesis of a *meso*-isomer with four chiral centers is rather complicated. Although a mixture of *dl*- and *meso*-isomers can be easily prepared by a nonstereoselective method, stereocontrolled synthesis of the *meso*-isomer is as difficult as that of the chiral isomer. Stepwise and stereospecific replacement reactions are required in both sides on the 2- and 6-positions of the pyridine ring. First, an (*S*)-alcohol of **(*R*OAc,SOH)-4** was mesylated and the resulting mesylate **11** was replaced with (*S*)-phenylethylamine inducing (*R*)- and (*S*)-chiral centers on the right of the pyridine ring to afford **12** in 88% yield (Scheme 6). The acetate of **12** was hydrolyzed, and the resulting alcohol was tosylated to give **13** in 78% yield in two steps. Finally, substitution of the tosylate with (*R*)-phenylethylamine gave *meso*-isomer **1e** in 84% yield. No specific rotation of **1e** was observed. The proton NMR chart became quite simple. Two sets of methine protons appeared at 3.84 and 3.76 ppm as a quartet. Four methyl groups were observed at 1.37 ppm as a doublet. On the other hand, the synthesis of another *meso*-isomer **1f** was performed in four steps from **11**. Treatment of **11** with (*R*)-phenylethylamine gave **14** in 84% yield. Then methanolysis of **14**, followed by tosylation gave **15** in 70% yield in two steps. The substitution of **15** with (*S*)-phenylethylamine eventually gave **1f** in 83% yield. This compound also showed no specific rotation. In its proton NMR, characteristic peaks appeared at 1.30 ppm for 6 protons of two methyl groups as a doublet and at 1.29 ppm for 6 protons of the other two methyl groups as a doublet. At 3.59 and 3.48 ppm, two of each methine protons appeared as a quartet.

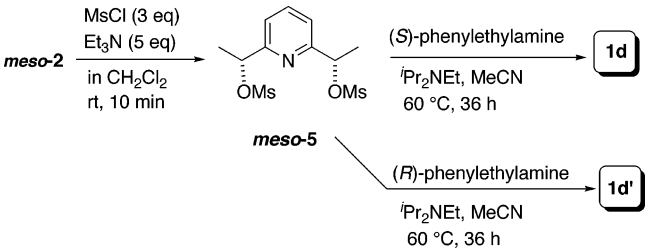
Structures of Six Diastereomers of 1a−f. In all compounds **1a−f**, no diastereomer can be observed in their proton and carbon NMR spectra, clearly indicating the high purity of the stereoisomers. Patterns of proton NMR chemical shifts of the 2,6-side chain part are characteristic for **1a−f**. The chemical shifts of four methyl groups and four methine groups are listed in Table 1. It is interesting that two 1,3-methine and two 1,3-methyl groups existing in syn-relation for **1b**, **1e**, and part of **1c** and **1d**, and those existing in an anti-relation for **1a**, **1f**, and part of **1c** and **1d** are easily identified. The chemical shifts of

SCHEME 4[a]



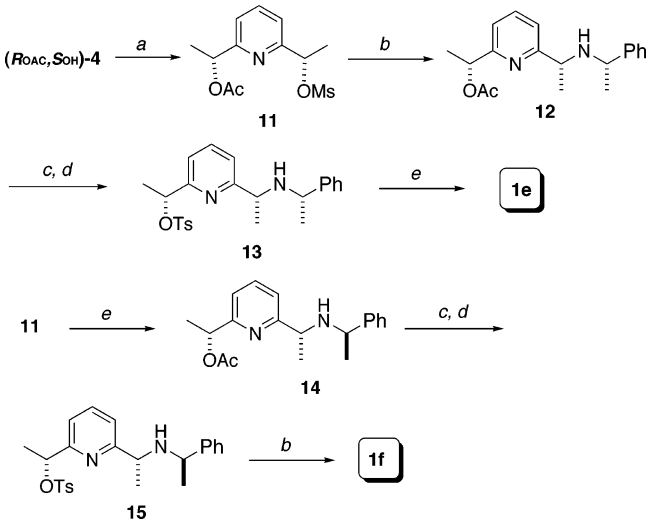
[a] Reagents and conditions: (a) MsCl (3 equiv), Et_3N (5 equiv), CH_2Cl_2, rt; (b) (*S*)-phenylethylamine (3 equiv), $^iPr_2NEt$ (5 equiv), CH_3CN, 60 °C; (c) (*R*)-phenylethylamine (3 equiv), $^iPr_2NEt$ (5 equiv), CH_3CN, 60 °C; (d) TsCl (1.2 equiv), Et_3N (1 equiv), DMAP (0.6 equiv), CH_2Cl_2, rt.

SCHEME 5



two methines in syn-relation appear in the range of 3.72−3.87 ppm and those in anti-relation appear in the range of 3.42−3.59 ppm. On the other hand, the chemical shifts of 1,3-dimethyl groups in syn-relation appear between 1.36 and 1.40 ppm and those in anti-relation appear between 1.19 and 1.30 ppm. Because compounds **1c** and **1d** have no C_2 symmetry, their four methines as well as their four methyls show different chemical shifts, while compounds having C_2 symmetry such as **1a** and **1b** or *meso*-compounds **1e** and **1f** indicate two kinds of methine protons. These proton NMR spectra suggest that the carbon

SCHEME 6[a]



[a] Reagents and conditions: (a) MsCl (3 equiv), Et_3N (5 equiv), CH_2Cl_2, rt; (b) (*S*)-phenylethylamine (3 equiv), $^iPr_2NEt$ (5 equiv), CH_3CN, 60 °C; (c) K_2CO_3 (3 equiv), MeOH; (d) TsCl (1.2 equiv), Et_3N (1 equiv), DMAP (0.6 equiv), CH_2Cl_2, rt; (e) (*R*)-phenylethylamine (3 equiv), $^iPr_2NEt$ (5 equiv), CH_3CN, 60 °C.

TABLE 1. Chemical Shifts of Methine and Methyl Protons for 1a−f

entry	compd	methine protons (ppm)		methyl protons (ppm)	
1	**1a**	3.58[a]	3.45[a]	1.30[b]	1.28[b]
2	**1b**	3.84[a]	3.72[a]	1.36[c]	
3	**1c**	3.87	3.74	1.40	1.39
		3.56	3.42	1.28	1.26
4	**1d**	3.86	3.76	1.40	1.39
		3.56	3.43	1.27	1.19
5	**1e**	3.84[a]	3.76[a]	1.37[c]	
6	**1f**	3.59[a]	3.48[a]	1.30[b]	1.29[b]

[a] Two protons. [b] Six protons. [c] Twelve protons.

chain of **1** takes an extended conformation in $CDCl_3$ solution. However, when a metal ion is added to **1**, triamine is able to coordinate with the metal ion to form a metal−triamine ligand complex. If the complex is formed, the molecule would take a holding conformation. In fact, when $ZnCl_2$ was added to the $CDCl_3$ solution of **1b**, these symmetric methyl and methine protons of **1b** shifted down to be 4.57 and 3.94 ppm for two kinds of two methines and 1.58 and 1.43 ppm for two kinds of two methyl groups. $ZnCl_2$−**1b** complex **16** was produced as nice crystals in 65% yield by the reaction of **1b** with $ZnCl_2$ in ethanol. The NMR spectrum of the resulting crystals in $CDCl_3$ exactly matched that observed in the mixture of **1b** and $ZnCl_2$. X-ray crystalographical analysis of the single-crystal clearly supported the holding structure of **16**, an ORTEP view of which is shown in Figure 3. It is found that the complex has a pincer-type structure with two newly generated (*S*)-chiral centers on the nitrogen atoms. Chiral pyridines have been recognized as an important ligand not only for asymmetric synthesis but also functional materials.[8] These chiral pyridine diamines will be expected to have such functional properties.

Conclusion

In summary, we have succeeded in stereodifferentiated synthesis of all the stereoisomers of 2,6-bis[1-(1-phenylethy-

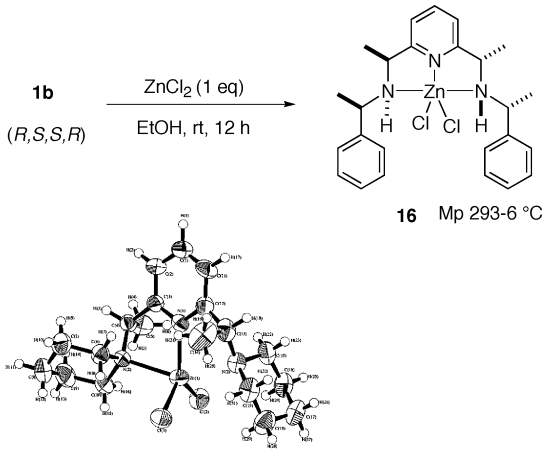


FIGURE 3. Synthesis and crystal structure of Zn complex **16**.

lamino)ethyl]pyridines **1a**−**f**. The synthesis involving stepwise or simultaneous stereospecific substitution of pyridinylethyl methansulfonate or toluenesulfonate with (*R*)- or (*S*)-phenylethylamine is highly efficient with high enantio- and diastereo selectivities to provide optically pure triamine molecules, which is found to exist as an extended conformation. Chiral Zn-triamine complex **16** was prepared and the absolute structure was revealed by the X-ray analysis. The approach for the stereoselective preparation of **1** is a good example of the systematic synthesis of complex molecules having multiple chiral centers.

Experimental Section

Mixture of *dl*- and *meso*-2,6-Bis(1-hydroxyethyl)pyridine (2).[7] To a solution of 2,6-bisacetylpyridine (13.0 g, 79.7 mmol) in MeOH (150 mL) was added $NaBH_4$ (2.00 g, 52.9 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with water and extracted with $CHCl_3$ a few times. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was distilled to give **2** (12.7 g) in 95% yield: colorless oil; R_f = 0.29 (70% EtOAc in hexane); bp 120−121 °C/2 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 7.7 Hz, 2H,), 4.90 (q, J = 6.6 Hz, 2H), 3.92 (brs, 2H), 1.51 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (2C), 137.7, 118.3 (2C), 69.1 (2C), 24.1 (2C); IR (film, cm^{-1}) 3292.

Lipase-Catalyzed Kinetic Acetylation of 2,6-Bis(1-hydroxyethyl)pyridine. A mixture of 2,6-bis(1-hydroxyethyl)pyridine (**2**) (4.48 g, 26.8 mmol), *Ca*l (Novozym 435) (2.69 g), MS 4A (8.8 g), and vinyl acetate (9.3 mL, 118 mmol) was stirred in ^{i}Pr$_2$O (350 mL) for 10 h at room temperature. The mixture was passed through a Celite pad, and the filtrate was condensed under reduced pressure. The crude residue was purified by column chromatography on silica gel eluted with 20% EtOAc in hexane to give **(*R*,*R*)-3** in 23% yield, with 50% EtOAc in hexane to give **(*R*OAc,*S*OH)-4** in 45% yield, and with EtOAc to give **(*S*,*S*)-2** in 23% yield.

(1′*R*,1″*R*)-2,6-Bis(1-acetoxyethyl)pyridine ((*R*,*R*)-3): colorless oil; R_f = 0.82 (EtOAc); $[\alpha]^{29}_D$ +138 (*c* 1.8, acetone), $[\alpha]^{29}_D$ +151 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 7.8 Hz, 2H), 5.91 (q, J = 6.6 Hz, 2H), 2.13 (s, 6H), 1.58 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (2C), 159.7 (2C), 137.2, 118.7 (2C), 72.8 (2C), 21.0 (2C), 20.5 (2C); IR (film, cm^{-1}) 1740.

(1′*S*,1″*S*)-2,6-Bis(1-hydroxyethyl)pyridine ((*S*,*S*)-2): colorless oil; R_f = 0.51 (EtOAc); $[\alpha]^{32}_D$ −59 (*c* 0.9, acetone), $[\alpha]^{29}_D$ −25 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (t, J = 7.7 Hz, 1H), 7.21 (d, J = 7.7 Hz, 2H), 4.90 (q, J = 6.6 Hz, 2H), 3.89 (brs, 2H), 1.51 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (2C), 137.7, 118.3 (2C), 69.1 (2C), 24.0 (2C); IR (film, cm^{-1}) 3366.

(1′*R*,1″*S*)-2-(1′-Acetoxyethyl)-6-(1″-hydroxyethyl)pyridine ((*R*OAc,*S*OH)-4): colorless oil; R_f = 0.67 (EtOAc); $[\alpha]^{29}_D$ +48 (*c* 0.7, acetone), $[\alpha]^{29}_D$ +89 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (t, J = 7.7 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 5.93 (q, J = 6.6 Hz, 1H), 4.87 (q, J = 6.6 Hz, 1H), 4.48 (brs, 1H), 2.13 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H), 1.49 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 162.5, 158.5, 137.4, 118.9, 118.2, 72.6, 68.5, 23.9, 20.9, 20.4; IR (film, cm^{-1}) 3418, 1737.

Preparation of (*R*,*R*)-2 and *meso*-2. A mixture of **(*R*,*R*)-3** or **(*R*OAc,*S*OH)-4** (1.0 mmol) and K_2CO_3 (3.0 mmol) was stirred in MeOH (10 mL) for 10 min at room temperature. The mixture was then diluted with water and extracted with $CHCl_3$. The organic extract was washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with EtOAc to give **(*R*,*R*)-2** in quantitative yield or ***meso*-2** in 79% yield.

(1′*R*,1″*R*)-2,6-Bis(1-hydroxyethyl)pyridine ((*R*,*R*)-2): colorless oil; $[\alpha]^{26}_D$ +27 (*c* 0.4, $CHCl_3$), $[\alpha]^{24}_D$ +62 (*c* 0.7, acetone). All of the spectroscopic data including ^{1}H NMR, ^{13}C NMR, IR, and MS are exactly same as those of (***S*,*S*)-2** except specific rotation.

meso*-2,6-Bis(1-hydroxyethyl)pyridine (*meso*-2):** white powder; mp 69−71 °C (EtOH). All of the spectroscopic data including ^{1}H NMR, ^{13}C NMR, IR, and MS are exactly same as those of (S*,*S*)-2**.

General Method for Mesylation: Preparation of 5. To a stirred solution of **2** (250 mg, 1.5 mmol) in CH_2Cl_2 (15 mL) were added Et_3N (1.05 mL, 7.5 mmol) and MsCl (0.35 mL, 4.5 mmol) at 0 °C. The mixture was stirred for 10 min at room temperature, diluted with water, and extracted with $CHCl_3$. The organic extract was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with 30% EtOAc in hexane to give **5** in quantitative yield.

(1′*R*,1″*R*)-2,6-Bis(1-methanesulfonyloxyethyl)pyridine ((*R*,*R*)-5): white powder; mp 75−77 °C (EtOH); R_f = 0.28 (50% EtOAc in hexane); $[\alpha]^{24}_D$ +121 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (t, J = 7.9 Hz, 1H), 7.45 (d, J = 7.9 Hz, 2H), 5.78 (q, J = 6.6 Hz, 2H), 2.98 (s, 6H), 1.76 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0 (2C), 138.3, 120.4 (2C), 80.1 (2C), 38.7 (2C), 21.6 (2C); IR (KBr, cm^{-1}) 1353, 1173; MS(CI) *m/z* 324 (M + H$^+$); HRMS calcd for $C_{11}H_{18}NO_6S_2$ (M + H$^+$) 324.0575, found *m/z* 324.0569. Anal. Calcd for $C_{11}H_{17}NO_6S_2$: C, 40.80; H, 5.47; N, 4.18. Found: C, 40.86; H, 5.30; N, 4.33.

(1′*S*,1″*S*)-2,6-Bis(1-methanesulfonyloxyethyl)pyridine ((*S*,*S*)-5): white powder; mp 75−77 °C (EtOH); $[\alpha]^{26}_D$ −112 (*c* 0.1, $CHCl_3$). All of the spectroscopic data including ^{1}H NMR, ^{13}C NMR, IR, and MS are exactly same as those of (***R*,*R*)-5** except specific rotation.

meso*-2,6-Bis(1-methanesulfonyloxyethyl)pyridine (*meso*-5):** white powder; mp 48−49.5 °C (EtOH). All of the spectroscopic data including ^{1}H NMR, ^{13}C NMR, IR, and MS are exactly same as those of (R*,*R*)-5**.

General Substitution Reaction of Mesylate with (*S*)- and (*R*)-Phenylethylamine: Reaction of 5. A mixture of **5** (1.0 mmol), ^{i}Pr$_2$NEt (5.0 mmol), and (*S*)- or (*R*)-phenylethylamine (3.0 mmol) in CH_3CN (5.0 mL) was heated at 60 °C for 23−36 h. After the reaction was completed, the mixture was diluted with water and extracted with $CHCl_3$. The organic extract was washed with saturated aq $NaHCO_3$ and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with 50% EtOAc in hexane to give **1a**, **1b**, **1d**, or their enantiomers.

(8) (a) Schulz, E. *Top. Organomet. Chem.* **2005**, *15*, 93−148. (b) Mamula, O.; von Zelewsky, A. *Coord. Chem. Rev.* **2003**, *242*, 87−95. (c) Chelucci, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2253−2383.

(1′*S*,1″*S*)-2,6-Bis{1-[(*S*)-1-phenylethyl]aminoethyl}pyridine (1a): 70% yield; colorless oil; $R_f = 0.30$ (EtOAc); $[\alpha]^{28}_D$ −249 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (t, J = 7.6 Hz, 1H), 7.34−7.21 (m, 10H), 6.92 (d, J = 7.6 Hz, 2H), 3.58 (q, J = 6.6 Hz, 2H), 3.45 (q, J = 6.6 Hz, 2H), 1.89 (s, 2H), 1.30 (d, J = 6.6 Hz, 6H), 1.28 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 (2C), 145.5 (2C), 136.4, 128.4 (4C), 126.9 (4C), 126.9 (2C), 120.0 (2C), 56.2 (2C), 55.8 (2C), 25.1 (2C), 23.6 (2C); IR (film, cm^{-1}) 3319; MS (FAB) *m*/*z* 374 (M + H^+); HRMS calcd for $C_{25}H_{32}N_3$ (M + H^+) 374.2596, found *m*/*z* 374.2603.

(1′*R*,1″*R*)-2,6-Bis{1-[(*R*)-1-phenylethyl]aminoethyl}pyridine (1a′): 81% yield; colorless oil; $[\alpha]^{26}_D$ +240 (*c* 0.07, $CHCl_3$).

(1′*S*,1″*S*)-2,6-Bis{1-[(*R*)-1-phenylethyl]aminoethyl}pyridine (1b): 75% yield; colorless oil; $R_f = 0.30$ (EtOAc); $[\alpha]^{28}_D$ −60 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, J = 7.7 Hz, 1H), 7.25−7.06 (m, 10H), 7.01 (d, J = 7.7 Hz, 2H), 3.84 (q, J = 6.6 Hz, 2H), 3.72 (q, J = 6.6 Hz, 2H), 2.01 (s, 2H), 1.36 (d, J = 6.6 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (2C), 145.7 (2C), 136.6, 128.3 (4C), 126.8 (2C), 126.8 (4C), 119.2 (2C), 55.9 (2C), 55.2 (2C), 23.1 (2C), 22.0 (2C); IR (film, cm^{-1}) 3314; MS (FAB) *m*/*z* 374 (M + H^+); HRMS calcd for $C_{25}H_{32}N_3$ (M + H^+) 374.2596, found *m*/*z* 374.2593.

(1′*R*,1″*R*)-2,6-Bis{1-[(*S*)-1-phenylethyl]aminoethyl}pyridine (1b′): 97% yield; colorless oil; $[\alpha]^{26}_D$ +62 (*c* 0.07, $CHCl_3$).

(1′*R,1″*S**)-2,6-Bis{1-[(*S*)-1-phenylethyl]aminoethyl}-pyridine (1d):** 75% yield; colorless oil; $R_f = 0.36$ (EtOAc); $[\alpha]^{23}_D$ −86 (*c* 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, J = 7.7 Hz, 1H), 7.33−7.17 (m, 10H), 7.04 (d, J = 7.7 Hz, 1H), 6.89 (d, J = 7.7 Hz, 1H), 3.86 (q, J = 6.6 Hz, 1H), 3.76 (q, J = 6.6 Hz, 1H), 3.56 (q, J = 6.8 Hz, 1H), 3.43 (q, J = 6.4 Hz, 2H), 2.35 (s, 2H), 1.40 (d, J = 6.6 Hz, 3H), 1.39 (d, J = 6.6 Hz, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 163.8, 145.8, 145.6, 136.5 (3C), 128.3 (2C), 126.9 (2C), 126.8 (2C), 126.6 (2C), 119.8, 119.2, 56.1, 55.7, 55.7, 55.2, 25.1, 23.6, 23.5, 21.9; IR (film, cm^{-1}) 3320; MS (FAB) *m*/*z* 374 (M + H^+); HRMS calcd for $C_{25}H_{32}N_3$ (M + H^+) 374.2596, found *m*/*z* 374.2602.

(1′*R,1″*S**)-2,6-Bis{1-[(*R*)-1-phenylethyl]aminoethyl}-pyridine (1d′):** 63% yield; colorless oil; $[\alpha]^{24}_D$ +83 (*c* 0.50, $CHCl_3$).

(1′*R*,1″*R*)-2-(1′-Hydroxyethyl)-6-[1″-(*p*-toluenesulfonyloxy)-ethyl]pyridine (6). To a solution of **(*R*,*R*)-2** (670 mg, 4.0 mmol) in CH_2Cl_2 (40 mL) were added Et_3N (0.56 mL, 4.0 mmol), DMAP (294 mg, 2.4 mmol), and TsCl (917 mg, 4.8 mmol) at room temperature. The mixture was stirred for 45 min at room temperature, quenched with water, and extracted with $CHCl_3$. The organic extract was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with 50% EtOAc in hexane to give **6** (558 mg) in 44% yield. Elution with hexane gave 7% of ditosylate and that with EtOAc gave a recovery of **(*R*,*R*)-2** in 50% yield: colorless oil; $R_f = 0.41$ (50% EtOAc in hexane); $[\alpha]^{26}_D$ +82 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.65 (t, J = 7.9 Hz, 1H), 7.29−7.24 (m, 3H), 7.14 (d, J = 7.9 Hz, 1H), 5.61 (q, J = 6.6 Hz, 1H), 4.80 (q, J = 6.6 Hz, 1H), 4.17 (brs, 1H), 2.41 (s, 3H), 1.61 (d, J = 6.6 Hz, 3H), 1.44 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 156.9, 144.7, 137.8, 133.9, 129.7 (2C), 127.8 (2C), 119.2, 119.2, 80.4, 68.3, 24.0, 21.6, 21.5; IR (film, cm^{-1}) 3411, 1362, 1176; MS (CI) *m*/*z* 322 (M + H^+); HRMS calcd for $C_{16}H_{20}NO_4S$: 322.1113, found *m*/*z* 322.1104. Its enantiomer **6′** was obtained from **(*S*,*S*)-2** in 38% yield along with 7% of ditosylate and 35% of **(*S*,*S*)-2**: colorless oil; $[\alpha]^{26}_D$ −78 (*c* 0.3, $CHCl_3$).

(1′*R*,1″*S*)-2-(1′-Hydroxyethyl)-6-{1″-[(*R*)-1-phenylethyl]-aminoethyl}pyridine (7). The substitution reaction was performed by the general substitution method of mesylate. (*R*)-Phenylethylamine was used, and the reaction time was 10 h. An 80% EtOAc in hexane solution was used as an eluent for silica gel column chromatography. Compound **7** was obtained in 99% yield: colorless oil; $R_f = 0.16$ (EtOAc); $[\alpha]^{26}_D$ −26 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (t, J = 7.7 Hz, 1H), 7.27−7.17 (m, 5H), 7.11 (d, J = 7.7 Hz, 1H), 7.07 (d, J = 7.7 Hz, 1H), 4.84 (q, J = 6.6 Hz, 1H), 3.88 (q, J = 6.6 Hz, 1H), 3.77 (q, J = 6.6 Hz, 1H), 2.04 (brs, 1H), 1.48 (d, J = 6.6 Hz, 3H), 1.39 (d, J = 6.6 Hz, 3H), 1.38 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 162.1, 145.5, 137.2, 128.4 (2C), 126.9, 126.6 (2C), 119.7, 117.8, 68.4, 56.0, 55.3, 24.2, 23.4, 21.8. IR (film, cm^{-1}) 3315; MS(CI) *m*/*z* 271 (M + H^+); HRMS calcd for $C_{17}H_{23}N_2O$ (M + H^+) 271.1810, found *m*/*z* 271.1808. Its diasrtereomer **9** was obtained from **6′** with (*R*)-phenylethylamine in 91% yield: colorless oil; $R_f = 0.30$ (EtOAc); $[\alpha]^{25}_D$ +159 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (t, J = 7.7 Hz, 1H), 7.34−7.25 (m, 5H), 7.12 (d, J = 7.7 Hz, 1H), 7.00 (d, J = 7.7 Hz, 1H), 4.89 (q, J = 6.4 Hz, 1H), 3.62 (q, J = 6.6 Hz, 1H), 3.46 (q, J = 6.6 Hz, 1H), 1.51 (d, J = 6.4 Hz, 3H), 1.32 (d, J = 6.6 Hz, 3H), 1.29 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 162.5, 145.5, 137.1, 128.4 (2C), 126.9 (2C), 126.8, 120.2, 117.8, 68.4, 56.0, 55.6, 25.1, 24.3, 23.3; IR (film, cm^{-1}) 3315; MS(CI) *m*/*z* 271 (M + H^+); HRMS calcd for $C_{17}H_{23}N_2O$ (M + H^+) 271.1810, found *m*/*z* 271.1818.

(1′*S*,1″*R*)-2-{1″-[(*R*)-1-Phenylethyl]aminoethyl}-6-[1′-(*p*-toluenesulfonyloxy)ethyl]pyridine (8). A tosylation of **7** and **9** was carried out in a manner similar to that described for the synthesis of **6** and **6′**. Elution of the crude mixture with 50% EtOAc in hexane for column chromatography on silica gel gave **8** in 77% yield. **8**: colorless oil; $R_f = 0.52$ (EtOAc); $[\alpha]^{24}_D$ −61 (*c* 0.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.43 (t, J = 7.7 Hz, 1H), 7.16−7.08 (m, 8H), 6.97 (q, J = 7.7 Hz, 1H), 5.51 (q, J = 6.6 Hz, 1H), 3.74 (q, J = 6.6 Hz, 1H), 3.63 (q, J = 6.6 Hz, 1H), 2.31 (s, 3H), 1.51 (d, J = 6.6 Hz, 3H), 1.30 (d, J = 6.6 Hz, 3H), 1.24 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 157.8, 144.5 (2C), 137.1, 134.0, 129.6 (2C), 128.4 (2C), 127.8 (2C), 126.9, 126.7 (2C), 120.6, 118.5, 80.9, 60.4, 55.9, 55.4, 23.0, 21.9, 21.6; IR (film, cm^{-1}) 3319, 1364, 1177; MS(CI) *m*/*z* 425 (M + H^+); HRMS calcd for $C_{24}H_{29}N_2O_3S$ (M + H^+) 425.1899, found *m*/*z* 425.1908. Its diastereomer **10** was obtained from **9** in 75% yield: colorless oil; $R_f = 0.65$ (EtOAc); $[\alpha]^{23}_D$ +62 (*c* 0.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (t, J = 8.4 Hz, 2H), 7.57 (t, J = 7.7 Hz, 1H), 7.34−7.24 (m, 8H), 7.00 (d, J = 7.7 Hz, 1H), 5.63 (q, J = 6.6 Hz, 1H), 3.60 (q, J = 6.4 Hz, 1H), 3.43 (q, J = 6.4 Hz, 1H), 2.41 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H), 1.32 (d, J = 6.4 Hz, 3H), 1.29 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 158.3, 145.3, 144.5, 137.0, 134.0, 129.6 (2C), 128.4 (2C), 127.8 (2C), 126.9, 126.8 (2C), 121.0, 118.4, 80.9, 56.0, 55.7, 24.9, 23.5, 21.7, 21.6; IR (film, cm^{-1}) 3418, 1364, 1190, 1177; MS(CI) *m*/*z* 425 (M + H^+); HRMS calcd for $C_{24}H_{29}N_2O_3S$ (M + H^+) 425.1899, found *m*/*z* 425.1897.

(1′*S*,1″*S*)-2-{1-[(*R*)-1-Phenylethyl]aminoethyl}-6-{1-[(*S*)-1-phenylethyl]aminoethyl}pyridine (1c). The reaction of **8** (95 mg, 0.2 mmol) with (*S*)-phenylethylamine (0.10 mL, 0.66 mmol) was carried out by the general substitution method of mesylate. Purification by column chromatography eluted with 50% EtOAc in hexane gave **1c** (74 mg) in 79% yield: colorless oil; $R_f = 0.42$ (EtOAc); $[\alpha]^{27}_D$ −153 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (t, J = 7.7 Hz, 1H), 7.34−7.21 (m, 10H), 7.03 (d, J = 7.7 Hz, 1H), 6.89 (d, J = 7.7 Hz, 1H), 3.87 (q, J = 6.6 Hz, 1H), 3.74 (q, J = 6.6 Hz, 1H), 3.56 (q, J = 6.9 Hz, 1H), 3.42 (q, J = 6.6 Hz, 1H), 2.15 (s, 2H), 1.40 (d, J = 6.6 Hz, 3H), 1.39 (d, J = 6.6 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (2C), 145.6 (2C), 136.5, 128.4 (4C), 126.9 (4C), 126.7 (2C), 119.9, 119.3, 56.1, 56.0, 55.7, 55.3, 25.2, 23.7, 23.1, 22.0; IR (film, cm^{-1}) 3317; MS(FAB) *m*/*z* 374 (M + H^+); HRMS calcd for $C_{25}H_{32}N_3$ (M + H^+) 374.2596, found *m*/*z* 374.2602. Its enantiomer **1c′** was obtained from **10** with (*S*)-phenylethylamine in 91% yield: colorless oil; $[\alpha]^{27}_D$ +151 (*c* 1.2, $CHCl_3$).

(1′*R*,1″*S*)-2-(1′-Acetoxyethyl)-6-[1″-(methanesulfonyloxy)ethyl]pyridine (11). Mesylation of (***R*OAc,SOH)-4** (1.0 g, 4.8 mmol) was carried out by the general substitution method of mesylate.

Purification by silica gel column chromatography eluted with 50% EtOAc in hexane gave **11** (1.4 g) in quantitative yield: colorless oil; $R_f = 0.54$ (50% EtOAc in hexane); $[\alpha]^{30}_D$ +3 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (t, $J = 7.7$ Hz, 1H), 7.37 (d, $J = 7.7$ Hz, 1H), 7.30 (d, $J = 7.7$ Hz, 1H), 5.89 (q, $J = 6.6$ Hz, 1H), 5.77 (q, $J = 6.6$ Hz, 1H), 2.94 (s, 3H), 2.13 (s, 3H), 1.76 (d, $J = 6.6$ Hz, 3H), 1.57 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 160.0, 157.4, 137.7, 119.7, 119.3, 80.5, 72.6, 38.5, 21.4, 21.0, 20.4; IR (film, cm^{-1}) 1733, 1358, 1176; MS (CI) *m/z* 288 (M + H$^+$). HRMS calcd for $C_{12}H_{18}NO_5S$ (M + H$^+$) 288.0905, found *m/z* 288.0906.

Substitution of 11 with (*S*)-Phenylethylamine and (*R*)-Phenylethylamine. The reactions of **11** with (*S*)-phenylethylamine and (*R*)-phenylethylamine were carried out by the general substitution method of mesylate. Purification by column chromatography eluted with 80% EtOAc in hexane gave **12** in 88% yield and **14** in 84% yield, respectively.

(1′*R*,1″*R*)-2-(1′-Acetoxyethyl)-6-{1″-[(*S*)-1-phenylethyl]-aminoethyl}pyridine (12): colorless oil; $[\alpha]^{26}_D$ +85 (*c* 0.2, $CHCl_3$); $R_f = 0.21$ (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (t, $J = 7.7$ Hz, 1H), 7.27−7.18 (m, 5H), 7.14 (d, $J = 7.7$ Hz, 1H), 7.08 (d, $J = 7.7$ Hz, 1H), 5.90 (q, $J = 6.6$ Hz, 1H), 3.85 (q, $J = 6.6$ Hz, 1H), 3.75 (q, $J = 6.6$ Hz, 1H), 2.12 (s, 3H), 2.07 (s, 1H), 1.57 (d, $J = 6.6$ Hz, 3H), 1.38 (d, $J = 6.6$ Hz, 3H), 1.36 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 163.7, 159.6, 145.6, 136.9, 128.3 (2C), 126.7, 126.7 (2C), 119.9, 117.9, 73.1, 55.9, 55.2, 23.2, 22.0, 21.2, 20.6; IR (film, cm^{-1}) 3324, 1736; MS (CI) *m/z* 313 (M + H$^+$); HRMS calcd for $C_{19}H_{25}N_2O_2$ (M + H$^+$) 313.1916, found *m/z* 313.1922.

(1′*R*,1″*R*)-2-(1′-Acetoxyethyl)-6-{1″-[(*R*)-1-phenylethyl]-aminoethyl}pyridine (14): colorless oil; $[\alpha]^{30}_D$ +206 (*c* 0.9, $CHCl_3$); $R_f = 0.63$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (t, $J = 7.7$ Hz, 1H), 7.33−7.22 (m, 5H), 7.18 (d, $J = 7.7$ Hz, 1H), 6.98 (d, $J = 7.7$ Hz, 1H), 5.93 (q, $J = 6.6$ Hz, 1H), 3.58 (q, $J = 6.6$ Hz, 1H), 3.43 (q, $J = 6.6$ Hz, 1H), 2.14 (s, 3H), 1.98 (brs, 1H), 1.60 (d, $J = 6.6$ Hz, 3H), 1.27 (d, $J = 6.6$ Hz, 3H), 1.36 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 163.8, 160.1, 145.2, 136.9, 128.4 (2C), 126.4 (3C), 120.6, 118.1, 73.2, 56.2, 55.8, 24.9, 23.4, 21.3, 20.7; IR (film, cm^{-1}) 3422, 1734; MS (CI) *m/z* 313 (M + H$^+$); HRMS calcd for $C_{19}H_{25}N_2O_2$ (M + H$^+$) 313.1916, found *m/z* 313.1920.

Conversion of Acetates 12 and 14 to Tosylates 13 and 15. Compound **12** was treated with K_2CO_3 in methanol as described for the methanolysis of **(*R*,*R*)-3** and **(*R*OAc,*S*OH)-4** and tosylations of the resulting alcohols by the same manner described for the synthesis of **6** gave **13** in 78% yield and **15** in 70% yield respectively. Purification was made by silica gel column chromatography eluted with 50% EtOAc in hexane.

(1′*R*,1″*R*)-2-{1′-[(*S*)-1-Phenylethyl]aminoethyl}-6-[1″-(*p*-toluenesulfonyloxy)ethyl]pyridine (13): colorless oil; $[\alpha]^{27}_D$ +68 (*c* 0.40, $CHCl_3$); $R_f = 0.29$ (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, $J = 8.3$ Hz, 2H), 7.50 (t, $J = 7.7$ Hz, 1H), 7.26−7.20 (m, 7H), 7.16 (d, $J = 7.7$ Hz, 1H), 7.05 (d, $J = 7.7$ Hz, 1H), 5.59 (q, $J = 6.6$ Hz, 1H), 3.79 (q, $J = 6.6$ Hz, 1H), 3.72 (q, $J = 6.6$ Hz, 1H), 2.38 (s, 3H), 2.18 (s, 1H), 1.58 (d, $J = 6.6$ Hz, 3H), 1.36 (d, $J = 6.6$ Hz, 3H), 1.30 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 157.8, 145.4, 144.6, 137.1, 134.1, 129.6 (2C), 128.3 (2C), 127.8 (2C), 126.9, 126.8 (2C), 120.5, 118.4, 81.0, 55.9, 55.4, 23.2, 21.9, 21.7, 21.5; IR (film, cm^{-1}) 3422, 1364, 1189, 1177; MS(CI) *m/z* 425 (M + H$^+$); HRMS calcd for $C_{24}H_{29}N_2O_3S$ (M + H$^+$) 425.1899, found *m/z* 425.1919.

(1′*R*,1″*R*)-2-{1′-[(*R*)-1-Phenylethyl]aminoethyl}-6-[1″-(*p*-toluenesulfonyloxy)ethyl]pyridine (15): colorless oil; $[\alpha]^{24}_D$ +153 (*c* 0.30, $CHCl_3$); $R_f = 0.29$ (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, $J = 8.3$ Hz, 2H), 7.54 (t, $J = 7.7$ Hz, 1H), 7.32−7.19 (m, 8H), 6.95 (d, $J = 7.7$ Hz, 1H), 5.63 (q, $J = 6.6$ Hz, 1H), 3.51 (q, $J = 6.8$ Hz, 1H), 3.34 (q, $J = 6.6$ Hz, 1H), 2.39 (s, 3H), 1.95 (s, 1H), 1.61 (d, $J = 6.6$ Hz, 3H), 1.25 (d, $J = 6.6$ Hz, 3H), 1.20 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 158.1, 144.9, 144.3, 136.9, 133.9, 129.5 (2C), 128.3 (2C), 127.7 (2C), 126.8, 126.7 (2C), 120.9, 118.4, 80.9, 55.9, 55.5, 24.8, 23.2, 21.6, 21.4; IR (film, cm^{-1}) 3420, 1365, 1196; MS(CI) *m/z* 425 (M + H$^+$); HRMS calcd for $C_{24}H_{29}N_2O_3S$ (M + H$^+$) 425.1899, found *m/z* 425.1902.

Synthesis of 1e and 1f from 13 and 15. Substitution of **13** with (*R*)-phenylethylamine and that of **15** with (*S*)-phenylethylamine were carried out by general substitution method of mesylate. Purification by column chromatography eluted with EtOAc gave **1e** in 84% yield and **1f** in 83% yield, respectively.

(1′*R,1″*S**)-2-{1′-[(*S*)-1-Phenylethyl]aminoethyl}-6-{1″-[(*R*)-1-phenylethyl]aminoethyl}pyridine (1e):** colorless oil; $[\alpha]^{25}_D$ 0 (*c* 0.80, $CHCl_3$); $R_f = 0.30$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, $J = 7.7$ Hz, 1H), 7.34−7.18 (m, 10H), 7.02 (d, $J = 7.7$ Hz, 2H), 3.84 (q, $J = 6.6$ Hz, 2H), 3.76 (q, $J = 6.6$ Hz, 2H), 2.24 (brs, 2H), 1.37 (d, $J = 6.6$ Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (2C), 145.7 (2C), 136.6, 128.4 (4C), 126.8 (2C), 126.7 (4C), 119.0 (2C), 55.8 (2C), 55.1 (2C), 23.4 (2C), 21.8 (2C); IR (film, cm^{-1}) 3317; MS(FAB) *m/z* 374 (M + H$^+$); HRMS calcd for $C_{25}H_{32}N_3$ (M + H$^+$) 374.2596, found *m/z* 374.2590.

(1′*R,1″*S**)-2-{1-[(*R*)-1′-Phenylethyl]aminoethyl}-6-{1″-[(*S*)-1-Phenylethyl]aminoethyl}pyridine (1f):** colorless oil; $[\alpha]^{27}_D$ 0 (*c* 0.50, $CHCl_3$); $R_f = 0.67$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, $J = 7.7$ Hz, 1H), 7.35−7.24 (m, 10H), 6.90 (d, $J = 7.7$ Hz, 2H), 3.59 (q, $J = 6.8$ Hz, 2H), 3.48 (q, $J = 6.6$ Hz, 2H), 2.34 (s, 2H), 1.30 (d, $J = 6.8$ Hz, 6H), 1.29 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.1 (2C), 145.4 (2C), 136.4, 128.4 (4C), 127.0 (4C), 126.9 (2C), 120.0 (2C), 56.1 (2C), 55.8 (2C), 25.2 (2C), 23.6 (2C).; IR (film, cm^{-1}) 3319; MS(FAB) *m/z* 374 (M + H$^+$); HRMS calcd for $C_{25}H_{32}N_3$ (M + H$^+$) 374.2596, found *m/z* 374.2582.

Preparation of 16. A mixture of **1b** (100 mg, 0.27 mmol) and $ZnCl_2$ (36 mg, 0.27 mmol) in EtOH (2.0 mL) was stirred at room temperature for 12 h. After evaporation of the solvent, **16** was isolated in 65% yield (88 mg) as colorless crystals.

η^3-{(1′*S*,1″*S*)-2,6-Bis[1-((*R*)-phenylethylamino-κN)ethyl]-pyridine}zinc(II) chloride (16)*:* mp 293−296 °C (EtOH−CH_2Cl_2); $[\alpha]^{25}_D$ −80 (*c* 0.29, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (t, $J = 7.7$ Hz, 1H), 7.40−7.24 (m, 10H), 7.09 (d, $J = 7.7$ Hz, 2H), 4.57 (brq, $J = 6.8$ Hz, 2H), 3.94 (q, $J = 6.8$ Hz, 2H), 2.74 (brs, 2H), 1.58 (d, $J = 6.8$ Hz, 6H), 1.43 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (2C), 142.5 (2C), 141.0, 128.9 (4C), 127.5 (2C), 126.7 (4C), 121.2 (2C), 55.2 (2C), 53.1 (2C), 22.2 (2C), 21.8 (2C); IR (KBr, cm^{-1}) 3446; MS(FAB) *m/z* 508 (M + H$^+$); HRMS calcd for $C_{25}H_{32}N_3Cl_2Zn$ (M + H$^+$) 508.1265, found *m/z* 508.1264. Anal. Calcd for $C_{25}H_{31}Cl_2N_3Zn$: C, 58.90; H, 6.13; N, 8.24. Found: C, 58.54; H, 6.19; N, 8.12.

Crystallographic Data: empirical formula, $C_{25}H_{31}Cl_2N_3Zn$; crystal system, monoclinic; space group, C_2 (#2); lattice parameters, $a = 11.689(1)$ Å, $b = 9.363(1)$ Å, $c = 11.234(1)$ Å, $\beta = 99.153(7)°$; $V = 1213.8(2)$ Å^3; *Z* value, 2; D_{calc}, 1.395 g/cm^3; (Cu Kα), 35.51 cm^{-1}; residuals, $R = 0.043$; $R_w = 0.068$.

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Supporting Information Available: Copies of the ^{1}H and/or ^{13}C NMR spectra for compounds **1a**−**f**, **(*R*,*R*)-5**, **6**−**8**, ***meso*-5**, and **9**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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